UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF

PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

DATE: September 20, 2001

MEMORANDUM

SUBJECT: **Diuron (PC Code 035505):**
Assessment of Mode of Action on Bladder Carcinogenicity

FROM: Yung G. Yang, Ph.D.
Reregistration Branch 2
Health Effects Division (7509C)

THRU: Pauline Wagner, Co-Chair
Mechanism of Toxicity Assessment Review Committee (MTARC)
Health Effects Division (7509C)
and
Karl Baetcke, Co-Chair
Mechanism of Toxicity Assessment Review Committee (MTARC)
Health Effects Division (7509C)

TO: William Burnham, Senior Science Advisor
Chairman, Cancer Assessment Review Committee (CARC)
Immediate Office
Health Effects Division (7509C)

cc: Anna Lowit, Executive Secretary, MTARC
Diana Locke, Risk Assessor, RRB 2

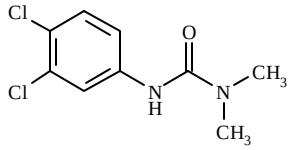
Action: The Registrant submitted a document entitled "Cancer Classification and Mechanism of Action of Diuron" and asked the Agency to reevaluate the cancer classification of diuron based on a proposed mode of action on bladder carcinogenicity. The MTARC is asked to review and determine the relevance of the proposed mode of action on bladder carcinogenicity for diuron.

Conclusion: A pre-screening subgroup of the MTARC has evaluated the proposed mode of action with the data submitted by the Registrant and concluded that the submitted information is **insufficient** to support a mode of action on bladder carcinogenicity for diuron.

I. Background

Diuron [3-(3,4-dichlorophenyl)-1,1-dimethylurea] is a substituted urea herbicide for the control of a wide variety of annual and perennial broadleaves and grassy weeds on both crop and noncrop sites. In 1997, the HED Carcinogenicity Peer Review Committee (CPRC) has classified diuron as a "known/likely" human carcinogen by all routes, based on urinary bladder carcinoma in both sexes of the Wistar rat, kidney carcinomas in the male rat (a rare tumor), and mammary gland carcinomas in the female NMRI mouse. The CPRC also recommended a low dose linear extrapolation model with Q_1^* of 1.91×10^{-2} $(mg/kg/day)^{-1}$ be applied to the animal data for the quantification of human risk, based on the urinary bladder carcinomas in the rat.

Empirical formula: $C_9H_{10}Cl_2N_2O$
Molecular weight: 233.1
CAS Registry No.: 330-54-1
PC Code: 035505



II. A Proposed Mode of Action on Bladder Carcinogenicity for Diuron

The Registrant stated that the tumorigenesis of diuron does not represent an expression of primary carcinogenic potential by diuron or its metabolites, it represents a concurrence of factors such as a high dose, dietary influence, metabolism and urinary pH. The Registrant proposed several basic elements to support this mode of action. The first is the etiology of the lesion, the second is the role of diet and pH of the rat urine, the third is the actual metabolism of diuron and the fourth is the non-genotoxicity of diuron. Documents submitted by the Registrant to support this mode of action are as follows.

(1) Diuron Risk Assessment: Evaluation of Dietary Exposure (MRID# 44302002). Bogdanffy, M.S., 1997. Haskell Lab. No. HL-1997-00613. E. I. Du Pont de Nemours and Company.
(2) Oral Toxicity and Metabolism of Diuron in Rats and Dogs. Hodge et al., 1967. Fd. Cosmet. Toxicol. 5: 513-531.
(3) Study for Toxicity to Wistar Rats with Special Attention to Urothelial Alterations (Administration in Diet for 2, 4, 12, and 26 Weeks with Recovery). Schmidt and Karbe, 1987. unpublished data.
(4) Risk Assessment Based on High-Dose Animal Exposure Experiments. Cohen and Ellwen, 1992. Chem. Res. Toxicol. 5: 742-748.
(5) Induction of Hyperplasia in the Bladder Epithelium of Rats by a Dietary Excess of Acid or Base:

Implications for Toxicity/ Carcinogenicity Testing. Groot et al., 1988. Fd. Chem. Toxicol. 5: 425-434.
(6) Lack of Bladder Tumor Promoting Activity in Rats Fed Sodium Saccharin in AIN-76A Diet. Okamura et al., 1991. Cancer Research 51: 1778-1782.
(7) Mitogenic Effects of Propoxur on Male Rat Bladder Urothelium. Cohen et al., 1994. Carcinogenesis 15: 2593-2597.
(8) Rapid Induction of Hyperplasia in Vitro in Rat Bladder Explants by Elevated Sodium Ion Concentrations and Alkaline pH. Storer et al., 1996. Toxicol. Appl. Pharm. 138: 219-230.
(9) Tributyl Phosphate Effects on Urine and Bladder Epithelium in Male Sprague-Dawley Rats. Arnold et al., 1997. Fund. Appl. Toxicol. 40: 247-255.
(10) Species-Specific Mechanisms of Carcinogenesis. Swenberg et al. (Eds.), 1992. Mechanism of Carcinogenesis in Risk Identification. pp. 477-500.
(11) Tumors of the Kidney, Renal Pelvis and Ureter. Hard, G.C. (source not provided).
(12) Influence of Food Restriction and Body Fat on Life Span and Tumor Incidence in Female Outbred Han:NMRI Mice and Two Sublines. Rehm et al., 1985. Z. Versuchtierk 27: 249-283.
(13) The Interpretation of Equivocal or Marginal Animal Carcinogenicity Tests. Squire, R.A. 1989. Cell Biol. Toxicol. 5: 371-376.
(14) Micronucleus Induction by Diuron in Mouse Bone Marrow. Agrawal et al. 1996. Toxicol. Lett. 89: 1-4.
(15) Diuron: Micronucleus Test on the Mouse to Evaluate for Mutagenic Effect. Herbold, B. 1983. Report No. 11915, Bayer AG, Inst. of Toxicology.
(16) Diuron: Micronucleus Test on the Mouse. Herbold, B. 1998. Report no. PH-27204. Bayer AG Toxicology.
(17) Mouse Bone Marrow Micronucleus Assay of DPX-14740-194 (Karmex® DF). Biegel, L.B. 1995. Haskell Lab No. 682-95. E. I. Du pont de Nemours and Company.
(18) Mouse Bone Marrow Micronucleus Assay of DPX-14740-200 (Karmex® 500 SC). Biegel, L.B. 1995. Haskell Lab No. 683-95. E. I. Du pont de Nemours and Company.
(19) Mouse Bone Marrow Micronucleus Assay of DPX-14740-205 (Karmex® 800 WP). Cox L.R. 1996. Haskell Lab No. 688-95. E. I. Du pont de Nemours and Company.

III. MTARC Response

A pre-screening MTARC (Karl Baetcke, Mike Ioannou, Anna Lowit, Pauline Wagner, and Yung Yang) reviewed the available information and concluded that the submitted information is **insufficient** to support a mode of action on bladder carcinogenicity for diuron based on the following reasons:

(1) The Registrant claimed that a mechanism or mode of action document (MRID# 44302002) has been submitted to the Agency without being reviewed by the CPRC. The pre-screening committee

reviewed the document and found that the document is only a report of an analysis using two models (quantal polynomial multistage and Weibull models) to evaluate carcinogenic risk to human of dietary exposure to diuron. This study was not designed to nor was it intended to address a mode of action on bladder carcinogenicity of diuron.

(2) A study entitled "Study for toxicity to Wistar rats with special attention to urothelial alterations by Schmidt and Karbe (1987), unpublished data" indicated that male Wistar rats were fed diuron in their diet at a concentration of 2500 ppm for 2, 4, 12, or 26 weeks. Recovery groups were similarly treated for 4 or 26 weeks and then observed for 4-8 weeks. Histopathological examination of urinary bladders revealed a treatment-related increased incidence of hyperplasia of the epithelium and an increase in the degree of hyperplasia from a treatment duration of four weeks onwards. Examination of animals in the recovery groups revealed a clear trend toward reversibility of the induced alterations after cessation of treatment. The pre-screening committee concluded that this study suggested a reversibility of possible precancerosis but did not present or propose a mode of action on bladder carcinogenicity for diuron.

(3) The Registrant submitted published literature in an attempt to address the role of diet and pH of the rat urine for supporting the mode of action on bladder carcinogenicity of diuron. The pre-screening committee reviewed these literature reports and determined that these reports were either non-diuron specific or irrelevant to diuron. The Registrant did not provide direct evidence to support a mode of action on dietary influence and high pH value as the mechanism on bladder carcinogenicity for diuron.

(4) The Registrant cited a rat metabolism study on diuron (HED Doc. No. 012408) and stated that there are no common mechanisms among diuron, linuron, and propanil with regard to cancer endpoints. No further information was presented. The pre-screening committee determined that the Registrant did not demonstrate a relevance of the metabolism of diuron to mode of action on bladder carcinogenicity.

(5) In 1997, the CPRC report has indicated that diuron was only weakly positive (considered to be equivocal) in an *in vitro* cytogenetic study. The Registrant submitted several reports on mouse bone marrow micronucleus study to show that diuron is non-genotoxic. The pre-screening committee referred its decision to latest HIARC Report on mutagenicity (HED Doc. No. 014657, dated August 28, 2001). The HIARC report stated that "diuron was not mutagenic in bacteria or in cultured mammalian cells and no indication of DNA damage in primary rat hepatocytes was observed. There was weak evidence of an *in vivo* clastogenic response in Sprague Dawley rats in one study and statistically significant increases in cells with structural aberrations in a second study conducted with the same rat strain. The data from the latter study, however, were shown to fall within the historical control range." The pre-screening committee concurred with the Registrant that there is little or no

concern on mutagenic activity of diuron.

IV. MTARC Conclusion

The pre-screening MTARC concluded that the submitted information **is insufficient to support the proposed mode of action on bladder carcinogenicity for diuron at this time.**